The Industrial Ecology of Pharmaceutical Raw materials and Finished Products with an Emphasis on Supply Chain Management Activities

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Introduction

Pharmaceutical drugs are used for the benefit of human and animal health. Innovations in pharmaceutical research and development of new drugs have not only controlled life threatening diseases and improved the quality of life and productivity, but have also increased the average life expectancy during the past few decades. The pharmaceutical industry has become an important sector in the United States (US) economy over the past few decades. The importance of pharmaceutical sector is likely to increase as new drugs change the life expectancy of the aging population, greater use of drugs for preventive health care, development of therapies for hitherto little known or defined diseases, new therapies to circumvent resistance to antibiotics, and therapeutic advances currently realized from biotechnology-derived drugs, including drug design based on understanding of human biochemistry and genetic disposition (Genomics).

The use of pharmaceutical drugs for various therapeutic needs is widespread and the detection of the pharmaceutical chemicals in the nature is viewed with concern because of their biological activity, and their lipophillic nature and resistance to biodegradation. No measurable evidence of the impact of pharmaceutical chemicals in the environment on human health is currently available (Christensen, 1998). Buser et al (1999) pointed out that pharmaceutical compounds can reach detectable concentrations in rivers and lakes especially when manufacture and use of such compounds is large. The occurrence of pharmaceutical chemicals in natural waters of US and Europe has recently been extensively reviewed (Daughton and Ternes, 1999; Daughton, 2001; Ternes, 2001; Kolpin et al. 2002). The degradation, depletion and dilution processes have been explained to illustrate that the long-term impacts may be minimized in the environment due to

these processes (Velagaleti and Gill, 2001; Velagaleti et. al., 2002). The Food and Drug Administration (FDA) has the regulatory oversight to assess the environmental impact of new pharmaceutical entities (FDA, 1998) and the U.S. Environmental Protection Agency (EPA) has the regulatory oversight for pharmaceutical discharges into the environment (EPA, 1998). Velagaleti et al. (2002) have described the regulatory oversight by EPA and FDA of environmental release of pharmaceuticals from manufacture, use and disposal. Even with the regulatory oversight and low levels of detection of pharmaceutical chemicals in the environment and the lack of any demonstrated impact on human health due to such presence, several recent conferences addressed recently concerns related to the long-term effects of pharmaceutical residues in the environment on human and environmental health. The American Chemical Society (ACS)-sponsored symposium in spring of 2000 on “Pharmaceuticals and Personal Care Products – An Emerging Concern” (Daughton and Jones-Lepp, 2001), the Tulane Environmental Conference in March 2001 on “Pharmaceutical Discharges in Drinking Water” (Velagaleti et al. 2002), and the National Ground Water Association (NWGA)-sponsored symposium in October 2001 on “International Conference on “Pharmaceuticals and Endocrine Disrupting Chemicals in Water” illustrate a growing interest in this area.

The current Workshop on “Industrial Ecology of Particulate Materials” (Penn State, 2002) echoes similar interest on ecological impact of pharmaceuticals in the environment, although from a slightly different perspective. The use of supply chain management for minimization of waste and consequent reduction of environmental exposure has been emphasized in the Workshop guide. The Workshop also mandates a discussion on the hypothesis that industrial chemicals such as pharmaceuticals may often have their largest environmental impact during the particulate stage when they are the most soluble. Our presentation discusses industrial ecology of pharmaceutical chemicals in the context of the workshop focus as outlined below:

1. Background on importance of pharmaceutical sector to the US economy and health of population;
2. An overview of the life cycle of pharmaceutical drugs;

3. Particulate nature and water solubility of pharmaceutical chemicals;
4. Implementation of supply chain management activities during pharmaceutical drug manufacturing, use and disposal;
5. Environmental exposure during manufacture, use and disposal; and
6. Current regulatory oversight of environmental exposure and impact.

Background

The impact of pharmaceutical sector to the US economy and to the general health of the population is significant and is measurable. Leonhardt (2001) has written that a larger work force resulting from increased life expectancy leads to economic growth. For example, increase in life expectancy in 1970s and 1980s over the previous decades has been shown to add a value of $57 trillion to the US economy (Passell, 2001). Currently annual net gains of $2.4 trillion/year due to increased life expectancy are reported in the Pharmaceutical Industry Profile 2002. Pharmaceuticals account for <10% of the total health care costs in the US and yet there is strong evidence to suggest that the use of pharmaceutical drugs contribute significantly to the reduction in health care costs (PhRMA, 2002) through their disease prevention role. The pharmaceutical industry has employed ~250,000 personnel in the year 2000. In 1998 the industry purchased goods and services worth ~$128 billion. More than 3.1 billion prescriptions have been written in 2001. Including over the counter drugs, there are tens of thousands of variation to pharmaceutical drugs in use in the United States. Sales of pharmaceutical drugs in the United States for the year 2001 were 131 billion dollars and posted a double-digit growth each year since 1995. The industry showed significant revenue growth during the past 30 years - from 4.5 billion in 1970 to 131 billion in year 2001. Pharmaceutical sales tripled in a decade from 44 billion in 1991 to 131 billion in 2001 (PhRMA, 2002). The increase in sales reflects increased use of pharmaceutical drugs of diverse biological activity for various therapies during this period. This growth in sales has also seen a concomitant increase in investments in R&D by the industry with approximately 16 to 20% of sales invested in new drug development. As a result of this

investment, an astonishing number of new medicines are in development (Table 1). Approximately 46% of these new medicines being developed are targeted for older Americans (PhRMA, 2002), a growing sector of population with the onset of retirement of large baby boomer generation.

Life Cycle of Pharmaceutical Drugs

It is prudent to discuss the life cycle of pharmaceutical drug products (Figure 1) before evaluation of their ecological impact. The life cycle of a drug product primarily consists of the following steps: discovery of active pharmaceutical ingredient (API, also known as drug substance) with therapeutic value → synthesis of drug substance → characterization of API including but not limited to preformulation studies → excipient (raw material) selection → formulation of the drug substance into a drug product → pre-clinical animal studies [using good laboratory practice (GLP) regulations] → investigational new drug application (IND) submission to FDA → human clinical studies (phases 1 to 3) using drug products produced on a pilot scale under current good manufacturing practices (cGMP, referred to in the text as GMP) → new drug application (NDA) submission to FDA and its approval → scale-up and commercial production of drug substance and drug product → packaging and labeling → shelf-life assessment → marketing and distribution for human consumption → post-approval changes to manufacturing, packaging or labeling → disposal of unused or expired drug product. APIs are characterized fully during pre-formulation studies to understand their chemical and physical properties that may potentially impact formulation process. APIs are formulated into a drug product using excipients. Excipients aid in the processing of API to a finished dosage form (oral, dermal, injectable) and enhance stability and bioavailability. The interaction of the API and the excipients are studied during formulation to ensure physical and chemical compatibility between components and to address bioavailability, safety and effectiveness (USP, 2002). Pharmaceutical drug products are formulated and manufactured as various dosage forms, the objective of which is not only to

ensure the physical and chemical integrity of the dosage form, but also to ensure that the active drug substance in a drug product reaches its intended site in the body within a desired time for a desired therapeutic effect. Common pharmaceutical dosage forms presented alphabetically reflecting their diversity of form are: Aerosols; Capsules; Creams; Delivery Systems – Transdermal, Ocular, Intrauterine; Emulsions; Gels; Implants; Inhalations; Injections; Irrigations; Lozenges; Ointments; Pastes; Powders; Solutions – Oral, Topical, Otic, Ophthalmic; Suspensions - Oral, Topical, Otic, Ophthalmic, Strips, Suppositories, Tablets. Approximately 70% of the drugs consumed are solid oral dosage forms (tablets and capsules). These dosage forms can be used to illustrate a typical drug product manufacturing cycle. The amount of pharmaceutical excipients and active to be used for a solid dosage form (tablet or capsule) are generally determined during formulation development. Following a pilot scale manufacturing and validation of process for use in clinical trials and the approval of drug application, the manufacturing scale up is initiated and the scaled up process is validated. Typically manufacturing of a solid oral pharmaceutical drug involves weighing and blending of excipients and active, followed by granulation, compressing, coating of the product and finally packaging and labeling. The granulated material is compressed into tablets or filled into capsules. The tablets may be coated with a coating solution for better appearance and texture. Containers and closures appropriate to dosage form, and marketing and safety needs of the dosage form are used for packaging.

The manufacture, use and disposal of pharmaceutical excipients, APIs, and drug products have its ecological implications (Figure 1). The ecological implications are discussed in later sections.

Particulate Nature and Water Solubility of Pharmaceutical Chemicals

The Workshop guide emphasizes that in the manufacture of many industrial products, including but not limited to, pharmaceuticals use of particulate raw materials is common. These materials often have their greatest environmental impact during the particulate stage when they are most soluble in water (the current “Workshop Guide, Industrial Ecology of Particulate Materials”).

Since greater than 70% of pharmaceutical drugs consumed are of solid oral dosage type (e.g., tablets, capsules), and the majority of the constituents of a dosage form are particulate in nature (the APIs and excipients), the discussion on particulate matter and water solubility will focus on the solid dosage forms. The information is considered generally applicable to most other dosage forms. Many of the chemicals used in the manufacture of the solid dosage forms (API and the excipients) are particulate in nature. Solubility in water and particle size properties of pharmaceutical APIs and excipients are very important characteristics for solid oral dosage formulations. During the formulation development, In vitro tests are used to provide the profiles of solid dosage forms in order to assess the interactive effects of these properties on the bioavailability of the API in the human body, and to help predict therapeutic efficiency. In general, while large particle size helps optimize flow during the granulation process of solid dosage forms, smaller particle size of APIs contained in tablets or capsules are known to enhance dissolution and absorption. The rate of dissolution of an API in the drug product depends to a large extent on its solubility in the solvent phase (Bankar, 1992).

A significant number of APIs and excipients are insoluble to very slightly soluble in water. Lipinsky (2002) pointed out that poor aqueous solubility is an industry wide problem in drug discovery with 30 to 40% of the active compounds surveyed showing poor solubility. An evaluation of the top 25 most prescribed drugs published by RxList (2002) using the solubility information from Merck Index (2002) indicates that ~40% of the APIs used for various drug products have poor solubility (Table 2). The general characteristics of pharmaceutical excipients (including but not limited to particle size and water solubility) are described in Handbook of Pharmaceutical Excipients (APA, 1994). Among the important excipients listed for solid dosage forms in attached excipient tables (Table 3), nearly 52% are practically insoluble to insoluble and ~20% are soluble in water. In comparison, ~38% of emulsifying agents, excipients used in ointments, creams, and other emulsions are soluble in water. A large number of excipients used for the solid oral dosage forms are from natural products and are biodegradable in the environment. The solubilities of pharmaceutical chemicals (Pharmacopeial and National

Formulary substances) are provided in USP under “Description and Relative Solubility of USP and NF articles” (USP, 2002). The solubility is often indicated by the descriptive terms ranging from very soluble to practically insoluble or insoluble (Table 4). The data in excipient tables (Tables 3) suggest that there is no clear correlation between particle size and water solubility. The particle size of various APIs is not published in the literature and can vary based on the manufacturing process, so no relationship between particle size and water solubility could be established.

When pharmaceuticals enter the publicly owned treatment works (POTW), they become integral part of the particulate matter present in POTW sewage effluent and sludge. When they leave POTW environment as wastewater effluent and enter rivers or streams, they become part of particulates in aquatic environment (surface water, sediment). When the POTW sludge solids are added to agricultural soils, they become part of particulate matter in terrestrial (soil) environment. Particle size distribution, settling velocities and specific gravity have been considered the major factors affecting the settlement of pollutants. Shin et al. (2001) studied the pollutant characteristics such as particle size distribution and settling patters of various pollutants and observed that settling velocity profiles are proportional to the initial concentration of particles. We do not know the ecological significance of particle size of pharmaceutical chemicals or the interaction of pharmaceutical residues with the particulate material prevalent in various environmental compartments. Clearly, this appears to be an area for future investigations.

Supply Chain Management Activities During Manufacturing, Use and Disposal

Strategies for reduction of waste generation such as reduction and recycling of wastes (Frosch and Gallopoulos, 1989) are critical in reducing environmental impacts throughout the supply chain - manufacture, distribution, use and disposal of industrial chemicals. For pharmaceutical drug products, such supply chain management activities include return to supplier, salvaging,

reprocessing and disposal through land filling or incineration. For APIs and excipients, in addition to the above strategies, reclamation and recycling are also allowed. Such strategies and activities for waste reduction are embodied, although not by design, in the current Good Manufacturing Practice (GMP) regulations for excipients (USP, 2002), APIs (FDA, 2001), and for finished drug products (FDA, 1998). Compliance with GMP regulations indirectly leads to the implementation of supply-chain management strategies (reverse logistics). An overview of the manufacture, use and disposal of pharmaceutical chemicals is presented below with a focus on supply chain management activities and a summary provided in Figure 2.

Excipients

The reverse logistics activities for waste minimization for pharmaceutical excipients include reprocessing, reworking and reuse, which are permitted by GMPs for excipients. The United States Pharmacopeia (USP, 2002) in their guidance on GMPs for bulk pharmaceutical excipients states that solvents may be recovered and reused in the same process or reused in a different process. Mother liquors or filtrates containing recoverable amounts of excipients and/or reactants can also be recovered and reused. The excipient GMP guidance also states that the non-conforming excipient products may be reprocessed or reworked to meet specified requirements or destroyed. The reprocessing, reworking, as well as destruction of those excipients failing to meet specifications (generally disposed of in a landfill) minimize exposure of excipients to the environment. Excipients failing to meet specifications for pharmaceutical use, are down graded by their manufacturers to non-pharmaceutical uses, and when they fail the quality criteria for such use they may be disposed off into landfills. Manufacturers of drug products, who are the main customers for excipients, return excipients failing to meet the drug product manufacturing specification, to the manufacturer of excipients. GMPs allow reprocessing of such materials and their reuse if the quality criteria are met. If the quality criteria are not met after reprocessing, the material will be disposed off in a landfill. The disposal of rejected excipients into certified landfills will, therefore, contain any environmental exposure.

APIs

For APIs, raw material accountability during manufacturing (mass balance), recovery and reuse of solvents, reprocessing of intermediates and APIs, land filling or incineration of rejected materials are activities associated with reverse logistics for waste minimization. The manufacture of APIs involves the use of appropriate raw materials to derive the synthesis or process intermediates and eventual synthesis of crude APIs. Typically, the crude API is further processed through extraction, purification, crystallization, filtration and drying steps. The containment procedures during the synthesis/manufacturing processes of API are designed to ensure minimal or no release of chemicals into the environment. The GMP guidance for APIs (FDA, 2001) requires material accountability (mass balance) during manufacturing. Section VIIIA of this guidance states “Actual yields should be compared with expected yields at designated steps in the production process. Expected yields with appropriate ranges should be established…. Deviations associated with critical process steps should be investigated… ”. Section XIVA of guidance states “Intermediates of APIs failing to meet established specifications should be identified as such and quarantined. These intermediates or APIs can be reprocessed or reworked”. Section VIIIE defines use of residual materials “ Residual materials can be carried over into successive batches of the same intermediate or API if there is adequate control”. Returned APIs (from drug product manufacture) can also be reprocessed, reworked, or destroyed as appropriate. Recovery and reuse of solvents, reactants, intermediates or the API is considered acceptable (FAD, 2001). The rejected APIs and raw materials are normally land filled. Some rejected APIs such as those regulated by Drug Enforcement Agency (DEA) are incinerated.

Drug Products

Controls for the accountability (mass balance) of raw materials (API and excipients) are required under GMPs for drug product manufacture (FDA, 1995), which state: components for drug

product manufacturing shall be weighed, measured or subdivided as appropriate [Section 211.01(b)]. Weighing, measuring, or subdividing operations for components shall be adequately supervised ---- [Section 211.01(c)]. Actual yields and percentages of theoretical yield shall be determined at the conclusion of each appropriate phase of manufacturing, processing, packaging, or holding of the drug product (Section 211.103). GMPs allow reprocessing of drug products. As stated in Section 211.204 "A drug product may be reprocessed provided the subsequent drug product meets appropriate standards, specifications, and characteristics." GMPs allow salvaging of drug products. As stated in Section on 211.208 "Whenever there is a question whether drug products have been subjected to such conditions (i.e., improper storage conditions), salvaging operations may be conducted only if there is evidence from laboratory tests and assays that the drug products meet all applicable standards of identity, strength, quality and purity. For drug products, accountability, reprocessing and salvaging and land filling and incineration are the reverse logistics activities considered for waste minimization.

General Supply Chain Management Considerations for Waste Minimization

In pharmaceutical manufacture and use, waste minimization strategies in addition to those described above can be adopted if the following practices can be investigated in the key areas identified below.

Drug Development Strategies

1. Overuse of excipients for formulation ease – excipient use can be considerably reduced with innovative formulations resulting in cost-effective and ecologically sound manufacture
2. Limited use of chemistry to improve drug life cycles - optimization of API chemistry and chemistry of API-excipient interaction including but not limited to particle size, purity, and manufacturing controls could result in small dosages and less toxic environmentally-friendly products. API and excipient chemistry based on criteria such as chemical (hydrolysis and

photolysis) and biological degradation (in environmental matrices) to reduce ecological impacts for large volume drugs.

3. Limited use of biochemical pathways in overall design - biochemistry and gene targeted therapies vs. “Is it pharmacologically active”? This approach could reduce considerably the use of excipients and APIs.

Physician Prescribing, Patient Use and Inventory Control Strategies

1. Over prescribing of pharmaceuticals - research on minimal dose for optimal therapeutic effect and controls on over-prescribing will lead to resource conservation and waste minimization
2. Excessive ecological impact through poor use – incomplete (partial) use of prescription medication by patient populations results in poor out come (example: antibiotic resistance) and could lead to excessive disposal into the environment, which can be prevented through appropriate information dissemination.
3. Poor inventory control resulting in drug destruction due to shelf life limits – drug products with assurance of strength, identity and purity as defined by GMP are still discarded when they are past shelf life limits. Approval of extended shelf lives based on stability data could help waste minimization. Better computer controls of drug inventory can reduce excess inventory.

Impact of FDA Regulations

1. Batch vs. continuous production - higher level of start up and shut down for batch production increasing rejects/waste.
2. Onerous regulatory review of drugs – slow adoption and approval of formulation or process changes that could result in improved life cycles, cost-effective manufacture and waste reduction.

3. Disposal of drugs prior to loss of activity – stability requirements constrain shelf life of drug products that meet GMP requirements of identity, strength, purity. Flexible strategies will minimize wastes.

Despite the above described supply chain management controls for waste minimization in place, small amounts of pharmaceutical chemicals are discharged during their life cycle into the environment as explained below.

Environmental Exposure During Manufacture, Use and Disposal

The water solubility and other physical and chemical properties [n-octanol/water partition coefficient, vapor pressure, dissociation constant, Ultraviolet-visible (UV-vis) absorption spectrum, density, sorption/desorption] and degradation (hydrolysis, photolysis, biodegradation) potential profiles play an important role in the movement and distribution of chemicals between various environmental compartments with highly water-soluble chemicals more likely to be transported and distributed by hydrologic cycle than water-insoluble chemicals (Table 5). Water solubility also affects the extent to which a chemical may adsorb to particulate matter such as soil or sediment or cross a lipid-water interface (FDA, 1987). Such information is valuable in predicting the environmental behavior of APIs, excipients and pharmaceutical drugs. Potential pathways of environmental exposure and degradation and depletion mechanisms are discussed in this section.

Manufacture of Excipients, APIs and Drug Products

The manufacture of excipients, APIs and drug products involves the use of appropriate raw materials and processing steps to derive the end products. The containment procedures during the manufacturing processes are designed to ensure minimal or no release of chemicals into the environment. However, equipment cleaning is likely to release process residues from equipment into process waste effluent stream. Process wastes are generally treated on site to facilitate

biodegradation and chemical degradation so that the residue levels are reduced sufficiently for discharge into domestic municipal sewage system or direct discharges into rivers, streams or ocean. As shown in Figure 3, the municipal sewage is transported (during which time some chemical residues may degrade) and processed at publicly owned treatment works (POTWs). During POTW processing, biological (aerobic and anaerobic biodegradation) and chemical (hydrolysis and photolysis) degradation and partitioning (sorption/desorption) phenomena occur (Tables 5 and 6) leading to residue decline, depletion and partitioning. Wastewater effluents containing residues partitioned into this phase are released into rivers or streams, when they become part of aquatic environmental compartment and undergo considerable dilution (Velagaleti et al, 2002). Anaerobic digesters at POTW process the sludge solids and the processed sludge applied to agricultural lands as organic supplement (undergoing significant dilution) or it is land filled (terrestrial environmental compartment). The residues undergo degradation and depletion in aquatic and terrestrial compartments through various biological and chemical degradation processes as shown in Table 6. Process water flow and discharge for API and drug product manufacturing facilities are illustrated and summarized by Velagaleti et al. (2002).

Use of Pharmaceutical Drugs

Pharmaceutical drugs are used for the benefit of human and animal health. As shown in Figure 4, residues from human use reach POTW through domestic sewage. The drug residues from animal use reach terrestrial environmental compartment. The degradation and depletion mechanisms for these residues in environmental compartments are similar to that described above for manufacturing residues and are summarized in Table 6.

Disposal of Pharmaceutical Chemicals

Unused, expired or rejected drug products are disposed of by: manufacturers, pharmacies, hospitals, clinics, and the patient population. Pharmacies, hospitals, and clinics, which may buy the drugs from distributors or manufacturers in bulk return the expired or unused drugs to the

distributors who may dispose off in certified landfills or send them to manufacturer for disposal through incineration or landfill facilities; the DEA regulated drugs are, however, required to be incinerated. Manufacturers dispose of lots failing specification and rejected for distribution through similar disposal mechanisms. Patients dispose off unused or expired drug products through municipal solid waste system, which are disposed off mostly in certified landfills or in some municipalities incinerated for co-generation of power.

Current Regulatory Oversight of Disposal of Residues from Manufacturing, Use and Disposal

Manufacturing

The pharmaceutical manufacturing effluent limits guidelines are provided in U.S Environmental Protection Agency's (U.S EPA's) "Pharmaceutical Manufacturing Category Effluent Limitations Guidelines, Pretreatment Standards, and New Source Performance Standards" (EPA, 1998). In these regulations, EPA has identified five subcategories (A to E) of pharmaceutical manufacturing operations – fermentation (A); natural extraction (B); chemical synthesis (C); formulating, mixing and compounding (D); and research (E). Pretreatment standards for process effluents are also defined for each of these categories using Best Practicable Control Technology (BPT) and Best Available Technology (BAT) economically achievable, to reduce or eliminate toxic priority pollutants. New Source Performance Standards (NSPS) are established for new plants to have the opportunity to install the best and most efficient production processes and BAT wastewater treatment technologies to achieve stringent limits for conventional, non-conventional and toxic pollutants. Pretreatment standards for existing manufacturing sources (PSES) and new sources (PSNS) are designed to prevent discharge of pollutants that pass through, interfere with, or otherwise are incompatible with the operations of the POTWs (EPA, 1998). Pharmaceutical manufacturing facilities will require routine monitoring of effluents and must comply with limits established in the guidelines. The state and local regulatory authorities may also set limitations

for discharge of residues in process effluents for direct discharge into rivers, streams etc., or indirect discharge to POTWs. These regulations minimize environmental exposure.

Use

Human Health Drugs

Before human or animal health drugs are approved for use, the FDA requires submission of Environmental Assessment (EA) documentation as a part of the Chemistry, Manufacturing and Controls (CMC) section of New Drug Applications (NDA) for implementing the National Environmental Policy Act (NEPA) as contained in 21 CFR Part 25 (FDA, 1985). Categorical exclusions from submission of EA were granted if qualified under 21 CFR Part 25.24, and step by step guidance for preparation and submission of EA was provided in 21 CFR Part 25.31 (FDA, 1985). An Environmental Assessment Technical Assistance Handbook was published outlining the test procedures required for data generation in support of the EA submissions (FDA, 1987). After reviewing the EAs submitted by the pharmaceutical industry over a 10 year period (~1987-1997), FDA performed a retrospective review of the data submitted (FDA, 1997) and revised the requirements. The current guidelines for submission of EA documentation are published in FDA's "Guidance for Industry - Environmental Assessments of Human Drugs and Biologics Applications" (FDA, 1998). These guidelines require that an EA for a drug product be submitted if the Expected Introduction Concentration (EIC) at the point of entry into the aquatic environment is equal to or greater than one part per billion (1 ppb). The EIC is estimated based on the highest per year production estimate (at the time of application for approval of the drug), and is calculated using the following equation provided in FDA guidance document (1998): EIC = A x B x C x D, where A = kilograms per year produced for direct use as active moiety (maximum production/year in a 5-year production cycle based on marketing estimates); B = 1/liters per day entering the POTW, estimated as 1.214×10^{11}; C = year/365 days; and D = $10^9/\mu g/kg$ (conversion factor). If we assume an API is produced for a drug product manufacture at 44,500 kg/year, then the

equation can be applied to estimate EIC – 44,500 x 1/1.214 x 10^{11} x 1/365 x 10^{9} = 1.004 ppb. In this scenario (EIC of <1 ppb), submission of an EA will be required as stated in FDA guidance. Categorical exclusions are granted if EIC estimates are below 1 ppb. The FDA guidance describes exceptions to categorical exclusions as well as provisions for considering metabolism in human body while estimating production estimates (FDA, 1998), both of which may require prior consultations with FDA.

Animal Health Drugs

For animal health drugs, if the predicted environmental concentration (PEC) of drug residues in the soil is >100 ppb (Phase I determination) for non-aquatic food animals (EMEA, 2000), a Phase II study (EMEA, 1996) will be required to provide risk assessment. However, for aquatic use of animal health drugs (e.g., aquaculture) if PEC exceeds 1 ppb, a Phase II investigation will be triggered. These guidelines were formulated by EMEA in consultation with FDA and other regulatory agencies in the world and currently FDA regulations require compliance with these limits and regulations.

Disposal

Manufacturers of pharmaceutical drugs are responsible for disposition of rejected and returned drug products. Under the ultimate disposition status to destroy, most pharmaceutical compounds are disposed off through land filling or incineration. Bulk purchasers of drugs such as pharmacies, hospitals, clinics generally return the unused or expired drug products to the distributors or manufacturers for disposition who follow land filling or incineration. The controlled drug substances are generally disposed of through incineration. At homes, empty or partially empty containers with expired drug products are disposed of through solid waste management system (FDA, 1998), which normally include disposal in a certified landfill but occasionally in some municipalities' incineration for cogeneration of power.

Conclusions

- The particulate nature of pharmaceutical chemicals, especially the solid dosage and semi-solid forms has received considerable attention from the point of view of raw material and finished product quality, but little attention from the point of view of their ecosystem effects. The interaction of particulate matter of drug residues released into the environment and the particles of municipal sewage (human drugs) or soil particles (animal drugs), or the ecological significance, if any, of such interaction are not well known.

- The supply chain management for waste minimization, although by not design, is implicit in GMP regulations and guidances for pharmaceutical excipients, APIs and products. The supply chain management activities include recycling, reprocessing, and reworking during manufacture.

- The manufacture, use and disposal of pharmaceutical excipients, bulk drug substance, and finished product may result in environmental exposure, which are regulated by the effluent limitation regulations of EPA and use and disposal regulations of FDA.

- Little is known of actual risk associated with pharmaceutical chemicals detected in potable water. Since most excipients used in making drug products are of natural mineral or plant origin, environmental risks are likely to be minimal due to the excipient components. The very low levels of APIs that are detected in potable water in U.S. and Europe, present a challenge in quantifying ecosystem effects and risks. It appears special methodologies may be required for monitoring the long-term effects of various classes of APIs detected in the environment.

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Table 1. 1000 New Medicines in Development

Type of Therapy	Total New Medicines in Development	Breakdown by Therapeutic Category
AIDS	**88**	38 Antivirals; 15 AIDS-related cancers; 14 vaccines; 8 immunomodulators; 7 anti-infectives; 6 antifungals.
Cancer	**286**	68 for lung cancer; 59 for breast cancer; 55 for colon cancer; 52 for skin cancer; 52 for prostrate cancer.
Medicines for Children	**128**	21 vaccines; 19 for cardiovascular disease; 16 for infectious bacterial disease; 14 for psychiatric disorders; 13 for cystic fibrosis; 13 for asthma, 9 for skin disorders; 8 for genetic disorders; 8 for neurologic disorders; 7 for AIDS and AIDS-related diseases.
Heart Disease and Stroke	**89**	18 for strokes; 18 for congestive heart failure; 12 for peripheral vascular disease; 11 for hypertension; 11 for adjunctive therapies; 10 for hyperlipidemia; and 9 for heart attacks.
Neurologic Diseases	**156**	41 for pain; 34 for brain tumors; 24 for Alzheimer's; 17 for Parkinson's; 16 for multiplesclerosis; 14 for stroke; and 10 for migrane headaches.
Medicines for Older Americans	**225**	44 for respiratory/lung disorders; 23 for diabetes; 22 for rheumatoid arthritis; 21 for Alzheimer's; 20 for depression; 19 for gastrointestinal disorders; 18 for pain; 16 for skin conditions; 15 for Osteoporosis; 14 for bladder/kidney disorders; 13 for Parkinson's disease.

Source: PhRMA (2002)

Figure 1. Life Cycle of a Pharmaceutical Drug Product

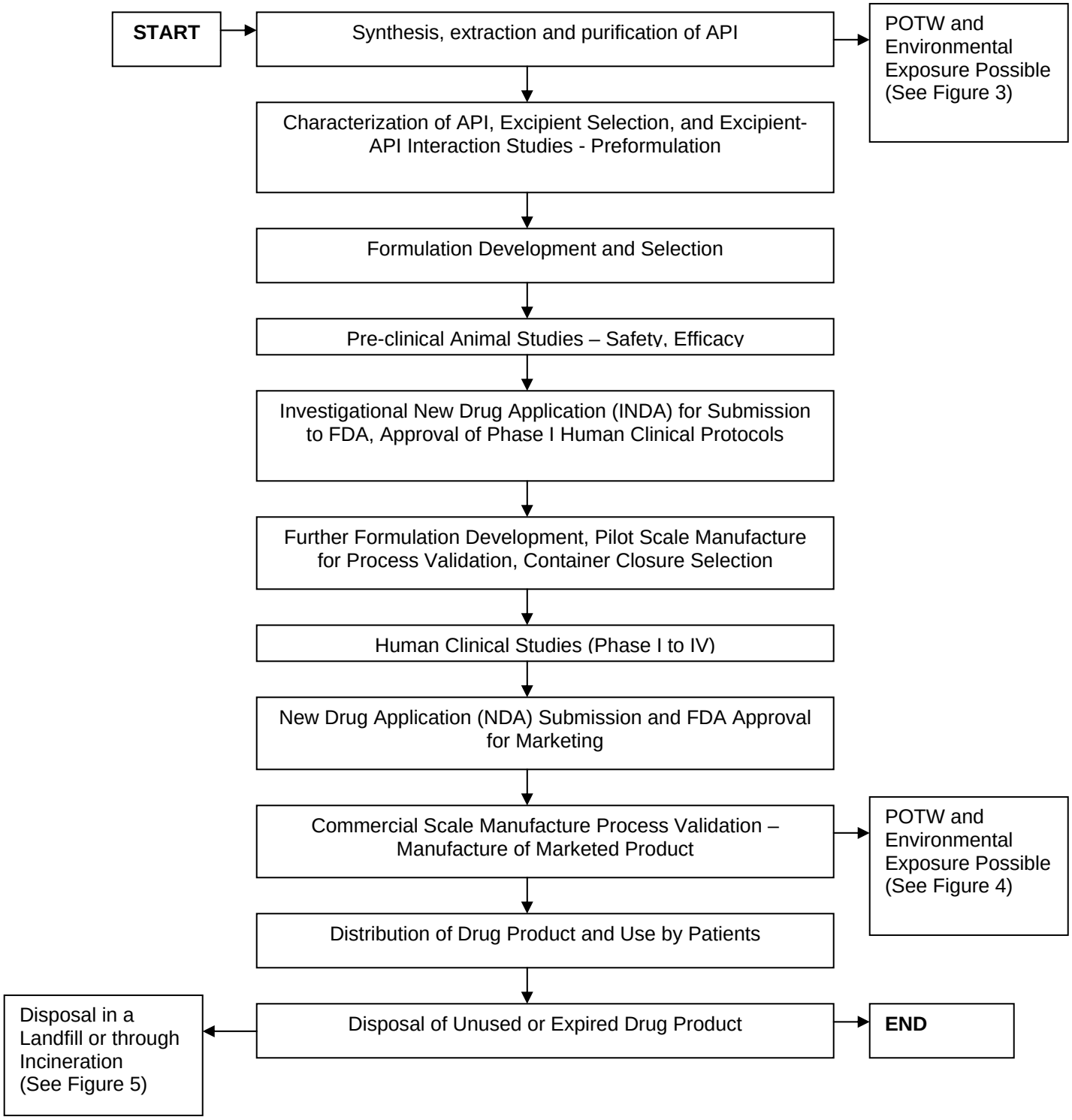

Table 2. Available Information for Water Solubility and Mice LD_{50} From the Merck Index (2001) for the Top 25 Most Prescribed Drugs in 2001 Published by the Internet Drug Index (2001)

Active Ingredient (Brand Name)	Solubility (mg/L)	LD_{50} for Mice (mg/Kg)
Hydrocodone with APAP		
- Hydrocodone	**Insoluble in water**	**85.7**
- APAP	**Very slightly soluble in cold water and considerably more soluble in hot water**	**338**
Atorvastatin calcium salt (Lipitor)	**NA**	**NA**
Conjugated Estrogens (Premarin)	**Estrogens in general are very slightly to practically insoluble to insoluble in water**	**NA**
Atenolol	**Slightly soluble in water**	**6200**
Levothyroxine (Synthroid)	**150**	**NA**
Azithromycin (Zithromax)	**NA**	**NA**
Furosemide	**Slightly soluble in water**	**2600 to 2820**
Amoxicillin	**4000 mg**	**NA**
Amlodipione (Norvasc)	**Slightly Soluble in Water**	**NA**
Alprazolam	**Insoluble in water**	**7200**
Albuterol (Albuterol Aerosol)	**Soluble in water**	**NA**
Loratidine (Claritin)	**NA**	**NA**
Hydrochlorothiazide	**Practically insoluble in water**	**8000**
Omeprazole (Prilosec)	**Very slightly soluble in water**	**4000**
Sertraline hydrochloride (Zoloft)	**3800**	**NA**
Paroxetine hydrochloride hemihydrate (Paxil)	**5400**	**NA**
Triamterene	**Slightly soluble in water**	**NA**
Lansoprazole (Prevacid)	**NA**	**NA**
Ibuprofen	**Relatively insoluble in water**	**1255**
Clecoxib (Celebrix)	**NA**	**NA**
Simvastatin (Zocor)	**30**	**NA**
Cephalexin	**NA**	**5000**
Metformin (Glucophage)	**Soluble in water**	**1000 (rats)**
Rofecoxib (Vioxx)	**NA**	**NA**
Lisinopril (Zestril)	**Relatively insoluble in water**	**NA**

Source: Data on top 25 drugs based on 3.1 billion prescriptions in 2001 from www.rxlist.com; Water solubility and LD_{50} data from Merck Index (13th edition; 2001).

Table 3. Common Pharmaceutical Excipients and Available Information on Particle Size and Water Solubility

Excipient	Function and Primary Use	Water Solubility	Particle Size (Median or Range)
DILUENTS			
Calcium carbonate	**Diluent for tablets, capsules**	**PIS**	**38 μm**
Calcium sulfate dihydrate	**Diluent for tablets, capsules**	**PRS**	**17 μm**
Compressible sugar	**Diluent, sweetener for tablets, capsules, primarily chewables**	**S - sucrose**	**75 μm to 425 μm**
Confectioner's sugar	**Diluent, sweetener for tablets, capsules**	**S - sucrose**	**14.3 μm**
Dextrates	**Diluent for tablets, capsules**	**S**	**211 μm**
Dextrin	**Thickener for suspensions; binder; tablet, capsule diluent**	**S – hot water**	**60 μm to 350 μm**
Dextrose	**Diluent for tablets (and binder in chewables) , capsules; tonicity and sweetening agent**	**MW**	**NA**
Dibasic calcium phosphate dihydrate	**Diluent for tablets, capsules**	**PIS**	**180 μm**
Glycerol palmitostearate	**Diluent and lubricant for tablets, capsules**	**PIS**	**NA**
Hydrogenated vegetable oil – type I	**Diluent, lubricant, and binder for tablets, capsules**	**PIS**	**50 μm to 70 μm**
Kaolin	**Diluent for tablets, capsules; suspending agent**	**PIS**	**0.6 μm to 0.8 μm**
α-Lactose	**Diluent for tablets, capsules**	**PRS**	**75 μm to 250 μm**
Magnesium carbonate	**Diluent for tablets, capsules**	**PIS**	**44.5 μm**
Magnesium oxide	**Diluent for tablets, capsules**	**PIS**	**45 μm**
Maltodextrin	**Diluent for tablets, capsules; binder, coating agent**	**S**	**75 μm to 250 μm**
Mannitol	**Diluent for tablets, capsules; tonicity and sweetening agent; vehicle for lyophilized preps**	**PRS**	**250 μm to 520 μm**
Microcrystalline Cellulose	**Diluent for tablets, capsules; tablet disintegrant**	**PRS**	**20 μm to 180 μm**
Polymethacrylates	**Diluent, binder and film-former**	**I to M**	**NA**
Potassium chloride	**Diluent for tablets, capsules; tonicity agent parenterals, ophthalamics**	**PRS**	**108 μm**
Powdered cellulose	**Diluent for tablets, capsules; tablet disintegrant; glidant**	**PIS**	**35 μm to 300 μm**
Pregelatinized starch	**Diluent and disintegrant for tablets, capsules; tablet binder**	**PRS**	**52 μm**
Sodium chloride	**Diluent for tablets, capsules; tonicity agent parenterals, ophthalamics**	**S**	**<30 μm**
Sorbitol	**Diluent for tablets, capsules; plasticizer; sweetening agent**	**S**	**125 μm to 590 μm**
Starch (corn, potato, rice, tapioca, wheat)	**Diluent and disintegrant for tablets, capsules; tablet binder; glidant**	**PIS**	**2 μm to 100 μm**
Sucrose	**Diluent and disintegrant for tablets, capsules; tablet binder**	**S**	**Crystals 540 μm; powder 64 μm**
Talc	**Diluent and lubricant for tablets, capsules, glidant**	**PIS**	**44 μm to 74 μm**
Tribasic calcium phosphate	**Diluent for tablets, capsules, glidant**	**PIS**	**180 μm to 350 μm**

I = Insoluble; PIS = Practically insoluble in water; PRS = Partially soluble; MW = Miscible with water; S = Soluble; NA = Not Available/Applicable.

Table 3 (Continued). Common Pharmaceutical Excipients and Available Information on Particle Size and Water Solubility

Excipient	Function and Primary Use	Water Solubility	Particle Size (Median or Range)
DISINTEGRANTS			
Alginic acid	**Tablet, capsule disintegrant and binder; thickening and suspending agent for pastes, creams, stabilizing agent for emulsions.**	**I**	**NA**
Carboxymethylcellulose calcium	**Tablet, capsule disintegrant and binder; viscosity-increasing and suspending agent for pastes, creams, stabilizing agent for emulsions.**	**I**	**73.7 μm**
Carboxymethylcellulose sodium	**Tablet, capsule disintegrant, binder; coating agent, viscosity-increasing and suspending agent for pastes, creams, stabilizing agent for emulsions.**	**S**	**NA**
Colloidal silicon dioxide	**Tablet disintegrant; glidant, viscosity-increasing and suspending agent for pastes, creams, anti-caking agent for aerosols.**	**PIS**	**7-16 nm**
Croscarmellose sodium	**Tablet, capsule disintegrant**	**I**	**44.5 μm to 73.7 μm**
Crospivodone	**Tablet disintegrant**	**PIS**	**50 μm to 400 μm**
Guar gum	**Tablet disintegrant, binder; viscosity-increasing and suspending agent for pastes**	**M**	**NA**
Magnesium aluminum silicate	**Tablet, capsule disintegrant, binder; viscosity-increasing and suspending agent for pastes, creams, stabilizing agent for emulsions.**	**PIS**	**260 μm to 636 μm**
Methyl cellulose	**Tablet, capsule disintegrant, binder; coating agent, viscosity-increasing emulsifying and suspending agent for pastes, creams, stabilizing agent for emulsions.**	**PIS in hot water Disperses In cold water**	**NA**
Polacrilin potassium	**Tablet, capsule disintegrant**	**PIS**	**70 μm to 250 μm**
Sodium alginate	**Tablet, capsule disintegrant and binder; viscosity-increasing and suspending agent for pastes, creams, stabilizing agent for emulsions.**	**PRS to viscous liquid**	**NA**
Sodium starch glycolate	**Tablet, capsule disintegrant**	**PIS**	**42 μm**
Microcrystalline Cellulose, powdered cellulose, pregelatinized starch and starch described under diluents	**Tablet disintegrants**	**See above in table**	**See above in table**

I = Insoluble; PIS = Practically insoluble in water; PRS = Partially soluble; MW = Miscible with water; S = Soluble; NA = Not Available/Applicable.

Table 3 (Continued). Common Pharmaceutical Excipients and Available Information on Particle Size and Water Solubility

Excipient	Function and Primary Use	Water Solubility	Particle Size (Median or Range)
GRANULATING AGENTS (BINDERS, ADHESIVES)			
Acacia	**Tablet binder; viscosity increasing, stabilizing and suspending agent for pastes, creams, stabilizing agent for emulsions.**	**PRS**	**NA**
See Dextrose, sucrose and starch under diluents	**Tablet binders**	**See Diluents**	**See Diluents**
Gelatin	**Tablet binder; frequently used for hard and soft gelatin capsules, viscosity-increasing, suspending, coating and gelling agent.**	**S in hot water**	**NA**
Povidone (PVP)	**Tablet binder, suspending agent**	**S**	**50 μm to 250 μm**
LUBRICANTS			
Calcium stearate	**Tablet and capsule lubricant primarily; also emulsifier, suspending and stabilizing agent**	**PIS**	**1.7 μm to 60 μm**
Glycerol monostearate	**Tablet and capsule lubricant; emollient, emulsifier, solubilizing and stabilizing agent**	**PIS**	**NA**
Glycerol palmitostearate	**Tablet and capsule lubricant and diluent**	**PIS**	**NA**
Hydrogenated castor oil	**Tablet and capsule lubricant; extended release and stiffening agent**	**I**	**≥1000 μm**
Hydrogenated vegetable oil, type I	**Tablet and capsule lubricant, diluent and binder**	**PIS**	**50 μm to 70 μm**
Light mineral oil and Mineral oil	**Tablet and capsule lubricant; emollient, solvent in ointments, emulsions, and lotions**	**PIS**	**NA**
Magnesium stearate	**Tablet and capsule lubricant**	**PIS**	**NA**
Polyethylene glycol	**Tablet lubricant and binder; suppository base; suspending and stabilizing agent for emulsions**	**S**	**NA**
Sodium benzoate	**Tablet and capsule lubricant, antimicrobial preservative**	**S**	**NA**
Sodium lauryl sulfate	**Tablet and capsule lubricant; emulsifying and wetting agent, anionic surfactant, detergent**	**S**	**NA**
Sodium stearyl fumarate	**Tablet and capsule lubricant**	**PRS**	**NA**
Stearic acid	**Tablet and capsule lubricant; emulsifying and solubilizing agent**	**PIS**	**NA**
Talc	**See under diluents in table above**	**See above**	**See above**
Zinc stearate	**Tablet and capsule lubricant**	**PIS**	**44.5 μm**

I = Insoluble; PIS = Practically insoluble in water; PRS = Partially soluble; MW = Miscible with water; S = Soluble; NA = Not Available/Applicable.

Table 4. Solubility Expression for Pharmaceutical Chemicals

Descriptive Term	Parts of Solvent Required for 1 Part of Solute
Very Soluble	**<1**
Freely soluble	**From 1 to 10**
Soluble	**From 10 to 30**
Sparingly Soluble	**From 30 to 100**
Slightly Soluble	**From 100 to 1000**
Very Slightly Soluble	**From 1000 to 10,000**
Practically Insoluble, or Insoluble	**More than 10,000**

Source: USP 25/NF 20 (2002) – Description and Relative Solubility of USP and NF Articles

Figure 2. Supply Chain Management (Reverse Logistics) Activities

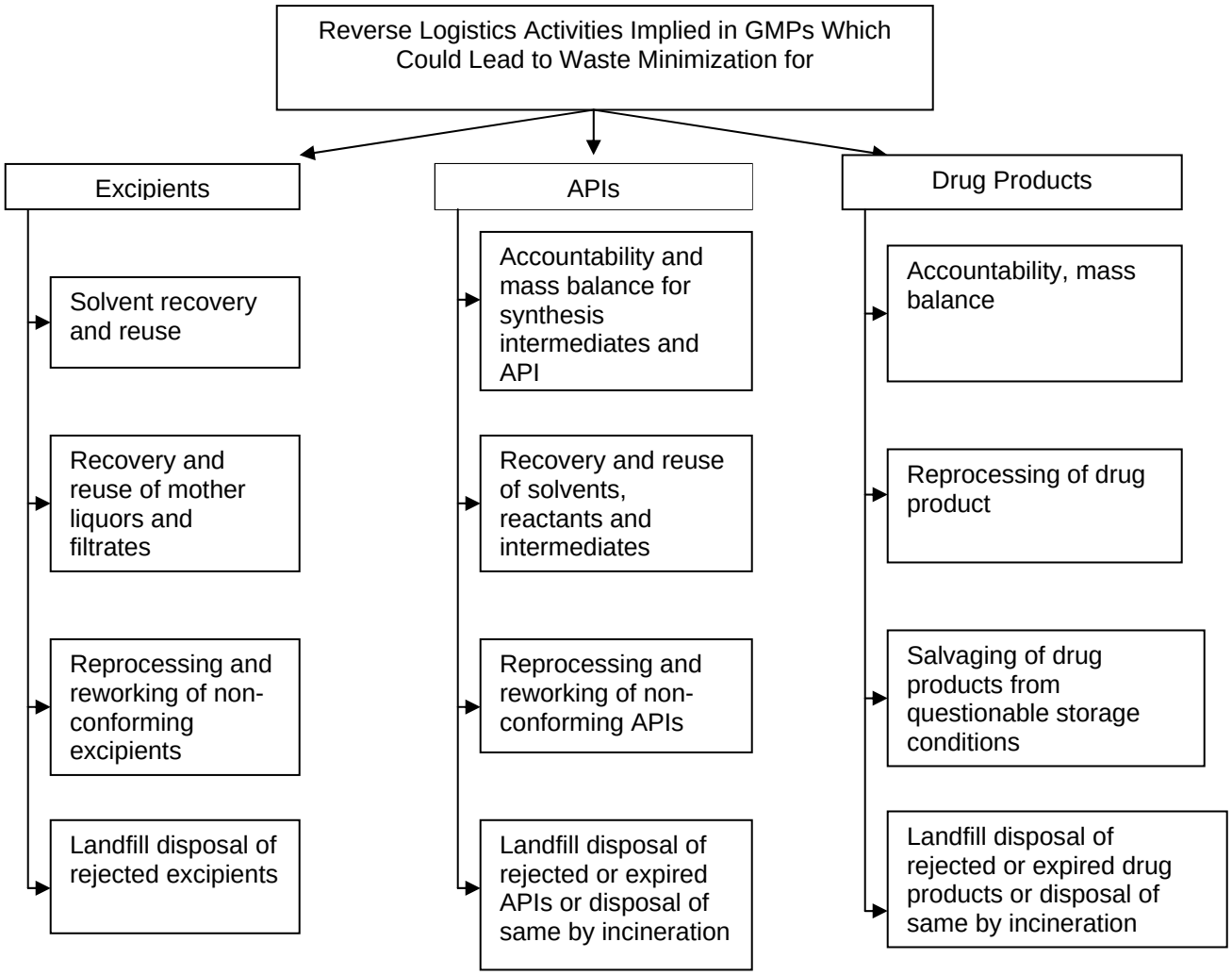

Table 5. Properties of Chemicals and their Significance in Ecological Distribution

Property	Significance
Water Solubility (S)	Chemicals that are water-soluble are likely to move and be distributed by hydrologic cycle between various environmental compartments than those that are relatively insoluble. They are also likely to be degraded in the environment through hydrolysis, photodegradation and biodegradation. Chemicals that are insoluble in water may also be distributed if they are stable in water and prone to evaporation (vapor transport) from water; however, such chemicals are likely to adsorb to particulate matter such as soil or sediment and in animals cross lipid (fat)-water interface.
n-Octanol/Water Partition Coefficient (Kow or log Kow)	Chemicals with low water solubility have a tendency to have high partition coefficient. High Kow value (Kow of 10^4 or log Kow of 4) indicates tendency of non-ionized organic chemicals to adsorb to soil or sediment and accumulate in fatty tissue of animals (bio-accumulation; bio-concentration).
Vapor Pressure	Chemicals with high vapor pressure have the potential to evaporate from soil and water, independent of their water solubility. High temperature and wind facilitate greater evaporation.
Dissociation Constant (pK)	A measure of pH-dependent ionization of chemicals in solution, pK determines the distribution of a chemical in ionized or non-ionized form in the environment. Ca^{++} and Mg^{++} ions that exist in natural waters combine with dissociated species to form insoluble precipitates. Positively charged ionized chemicals have a greater potential to bind to most soils, which are negatively charged. Non-ionized organic substances tend to pass through lipid membranes of animals and be metabolized.
Ultraviolet-Visible (UV-vis) Absorption Spectrum	Chemicals that have the ability to absorb energy from wavelengths in the UV-vis range of electromagnetic spectrum (290 to 800 nm) can undergo direct photochemical reaction resulting in degradation of chemicals in the environment.
Melting Temperature	Temperature at which the chemical's solid phase changes to liquid phase. The information on the physical state of a chemical helps assess the movement and potential for human and environmental exposure.
Density and Relative Density (Specific Gravity)	Density and relative density influence the distribution within aquatic environmental compartment. Chemicals with density greater than water tend to settle at the bottom and be part of the sludge/ sediment and undergo anaerobic degradation, those with density less than water tend to float and may be subject to light exposure and as a result photodegradation, and those with the same density as water tend to disperse at all levels and are likely to undergo chemical and biological degradation.
Sorption/Desorption	Chemicals with a strong tendency to adsorb to soil, sediment, or sludge are less likely to undergo chemical or biological degradation in contrast to those, which desorb. Desorbed chemicals may leach down the soil profile into ground water.
Hydrolysis	A common chemical degradation mechanism in aquatic matrix.
Photodegradation	Chemicals that absorb light in UV-vis spectrum range of 290-800 nm are likely to undergo direct photodegradation. Indirect photodegradation can result from a chemical receiving energy for degradation from another chemical that has absorbed sunlight (sensitizer/catalyst) or by reacting with products formed through direct photodegradation. Photodegradation is likely to occur in surface of soil and water.
Biodegradation	The main degradation mechanism in the environment whereby chemicals are significantly reduced in complexity through enzyme-catalyzed metabolic processes of microorganisms – predominantly bacteria and fungi. When completely biodegraded (to CO_2 and H_2O - mineralization), organic chemicals are depleted in the environment. The antibacterial antibiotics are likely to degrade by fungi present in the environment.

Table 6. Potential Degradation and Depletion of Pharmaceutical Chemicals

Degradation Mechanism	Matrix	Result
1. Metabolism	**Human/Animal Body (Dose Administered)**	**Absorption; Metabolism → partial (drug and its biotransformed products) or complete biotransformation (biotransformed products); drug and/or metabolites/biotransformed products → mineralization (e.g., small chain peptides) → expired CO_2 (depletion of drug residue due to expired CO_2)**
2. Aerobic Biodegradation	**On-site Treatment in Manufacturing Plants, Domestic Sewage, POTW, Surface Water, Soil, Landfills**	**Biodegradation → partial (drug and its biotransformed products) or complete biotransformation (biotransformed products); biotransformed products → mineralization → CO_2 (depletion of drug residue)**
3. Anaerobic Biodegradation	**On-site Treatment in Manufacturing Plants, Domestic Sewage, POTW Sludge, Deeper Soil Layer, Sediment, Ground Water, Landfills**	**Anaerobic Biodegradation → partial (drug and its biotransformed products) or complete biotransformation (biotransformed products); biotransformed products → CH_4 → CO_2 (depletion of drug residue)**
4. Chemical Degradation - Hydrolysis	**On-site Treatment in Manufacturing Plants, Domestic Sewage, POTW, Surface and Ground Water, Soil, Sediment, Landfills**	**Hydrolysis → partial degradation (drug + degradation product/s) or complete chemical degradation (degradation product/s)**
5. Chemical Degradation - Photolysis	**On-site Treatment in Manufacturing Plants, POTW, Surface Water, Soil Surface**	**Photolysis → partial degradation (drug + degradation product/s) or complete chemical degradation (degradation product/s)**

Figure 3. Manufacturing – Potential Exposure Pathways (Parentheses – Degradation Pathways in Table 6)

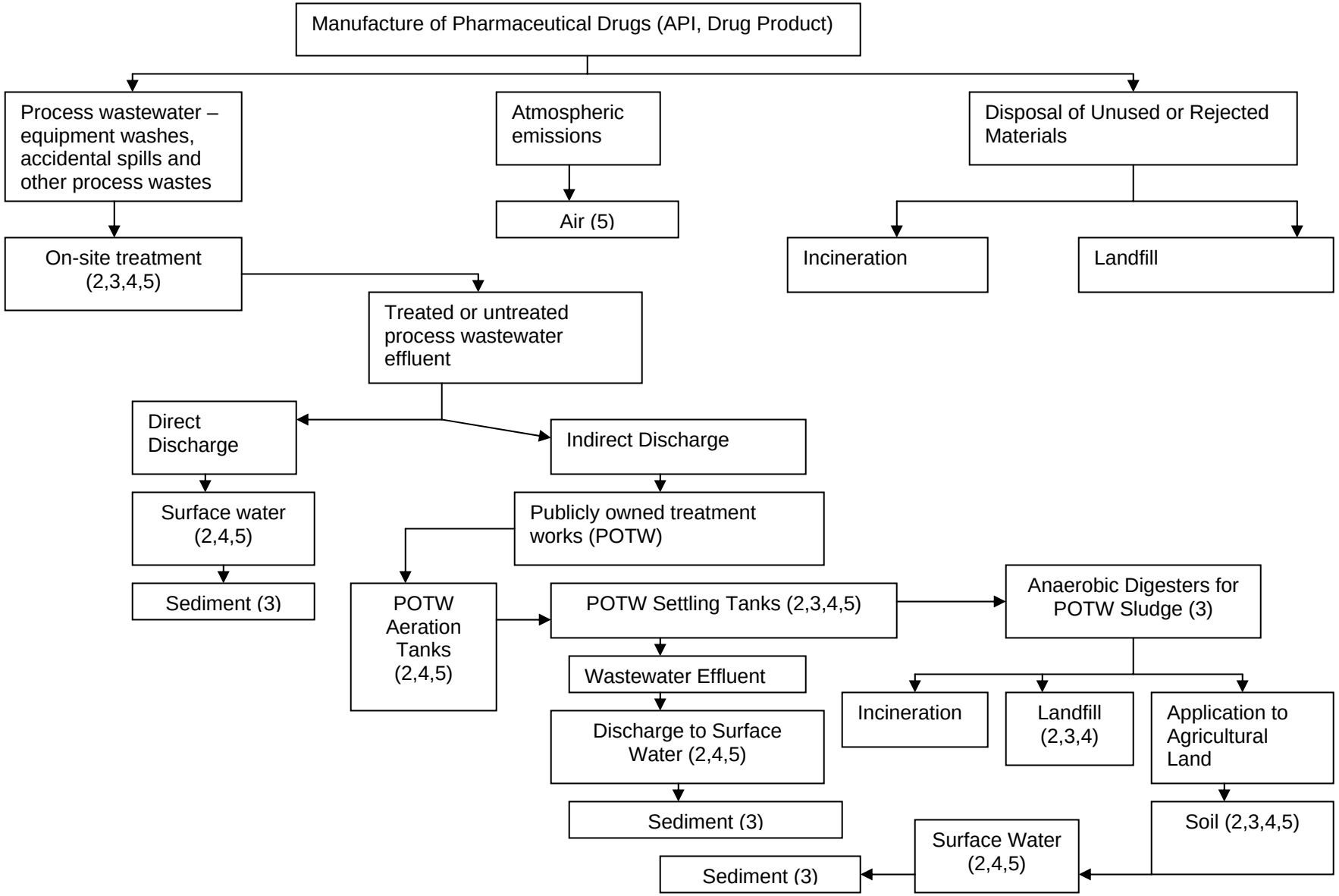

Figure 4. Use – Potential Exposure Pathways (Parentheses – Degradation Pathways in Table 6)

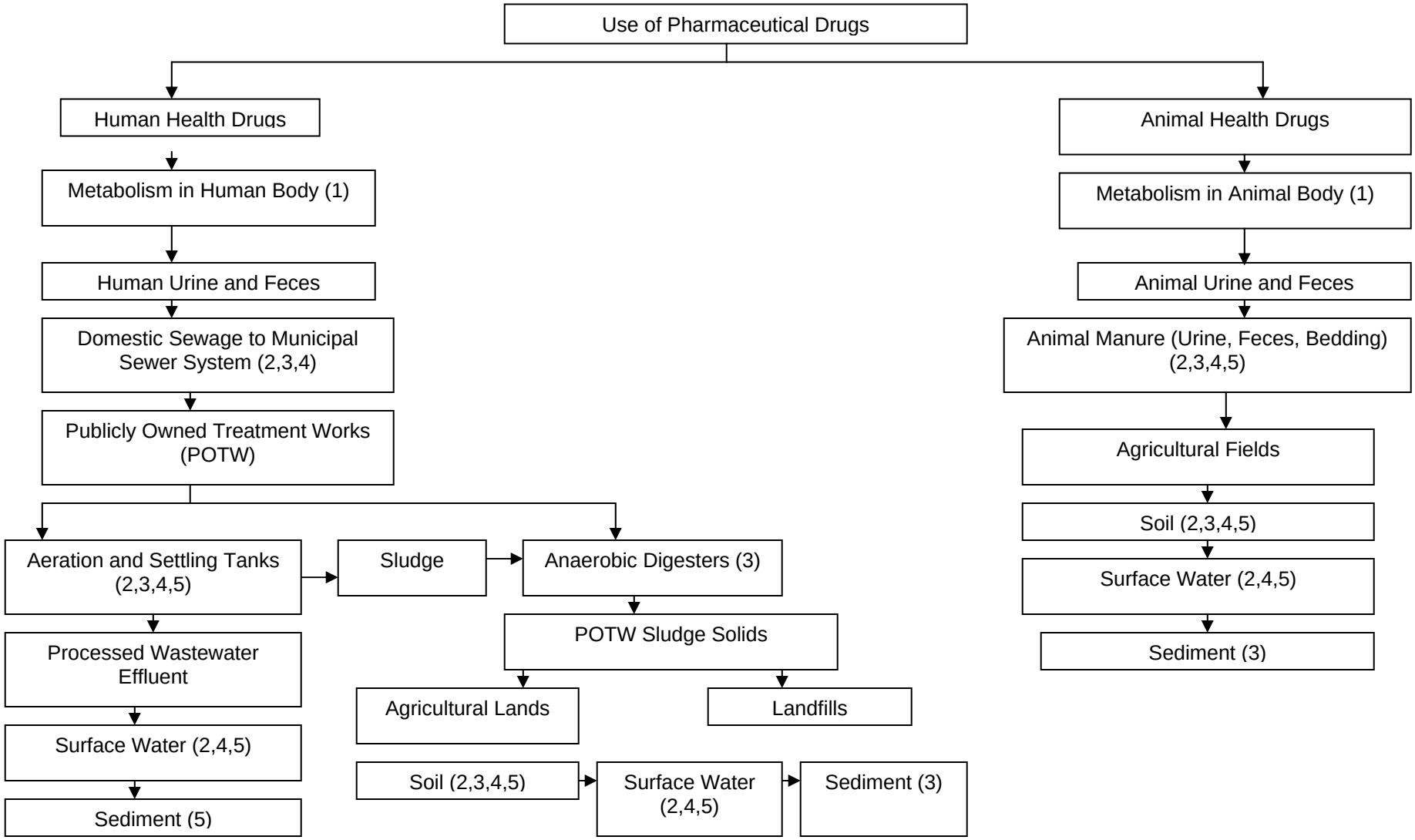

Figure 5. Disposal – Potential Exposure Pathways (Parentheses – Degradation Pathways in Table 6)